

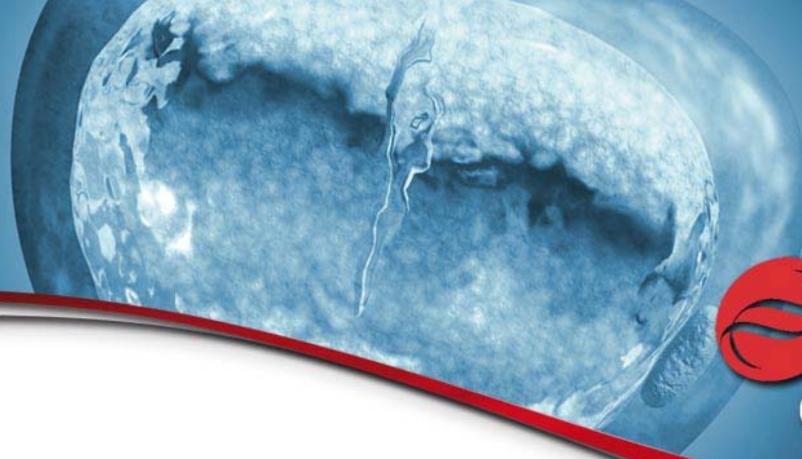


Reproduction

Inhibin B

Analyte Information





Inhibin B

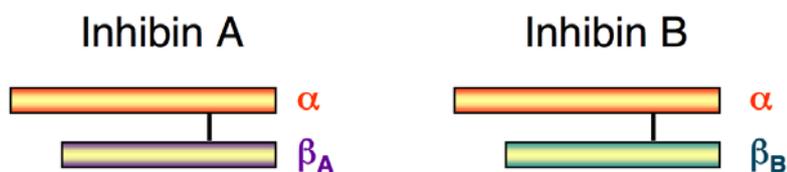
Introduction

Inhibins are polypeptides belonging to the transforming growth factor- β (TGF- β) superfamily which also includes TGF- β , activin glycoproteins and AMH (Anti-Müllerian hormone). All members of this family play a role in the growth and differentiation of tissues.

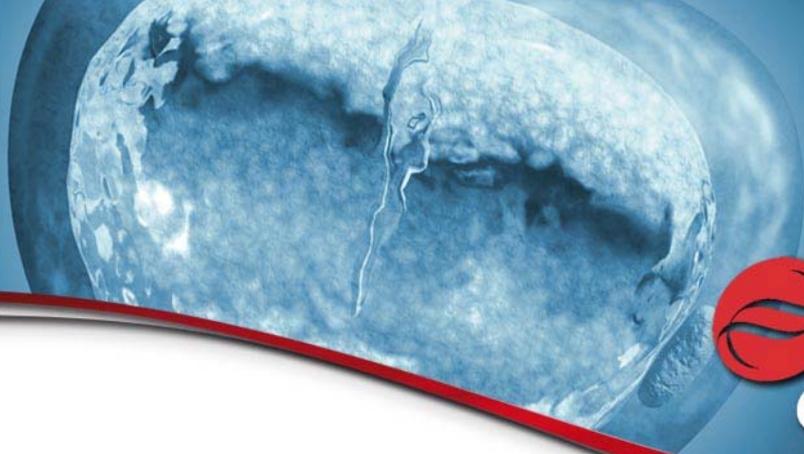
Inhibins are heterodimers consisting of a common α -subunit linked to either a β_A -subunit (inhibin A) or β_B subunit (inhibin B) by disulfide bridges (see Fig.1). Only the dimers have biological activity. Their molecular weight is approximately 32-36 kDa.

Free α -subunit forms are also present in circulation, and higher-molecular weight forms composed of α -subunits occur in follicular fluid and serum. Only the dimer form has biological activity, however¹.

Fig.1: Schematic diagram of inhibin structures



The black line between the monomers represents a disulfide bond.

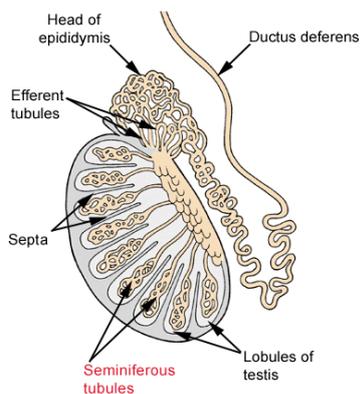


Biosynthesis

Inhibin B is produced in the Sertoli cells of the testis in the male, and in the granulosa cells of the ovary in the female (see Fig.2).

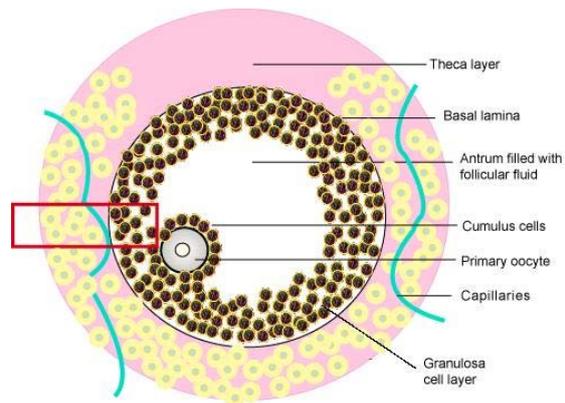
Fig.2: Inhibin B production

Section through Testis



90 % of the testis consists of seminiferous tubules which are tightly coiled. The walls of the seminiferous tubules are made up of endothelial cells called Sertoli cells.

Section through the Ovarian Follicle



Structure of the Graafian follicle. The granulosa cell layer is avascular, the vessels being excluded by the basal lamina which is laid down early in follicle life. The basal lamina protects the oocyte.

Physiological Function

Inhibins and activins are two closely related protein groups that have opposite biological effects. They are involved in the action of the hypothalamus – pituitary – gonadal axis. Activin (among other functions) enhances FSH biosynthesis and secretion. Conversely, inhibin B downregulates FSH synthesis by suppressing FSH production in pituitary gland, thereby controlling follicle growth and androgen production (see Fig.3).

Inhibin B also has local paracrine effects on the gonads.

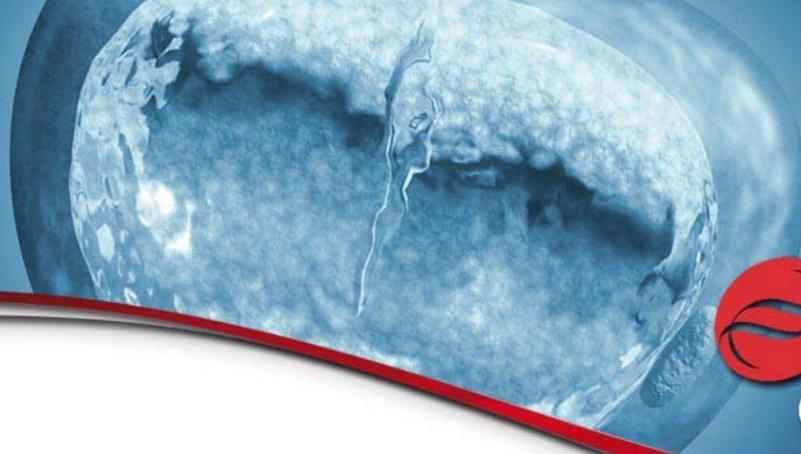
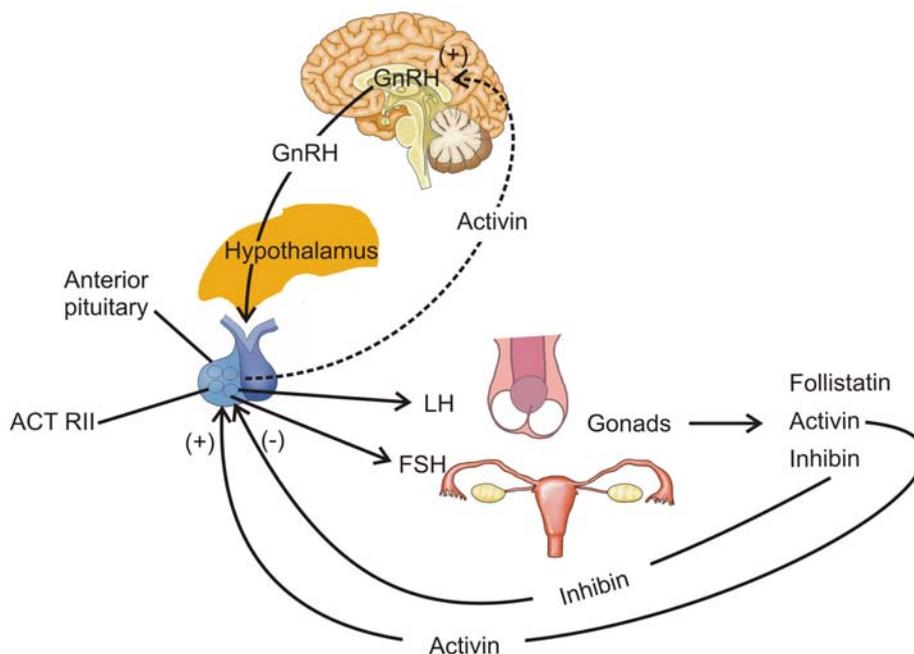


Fig.3: The hypothalamic - pituitary - gonadal axis



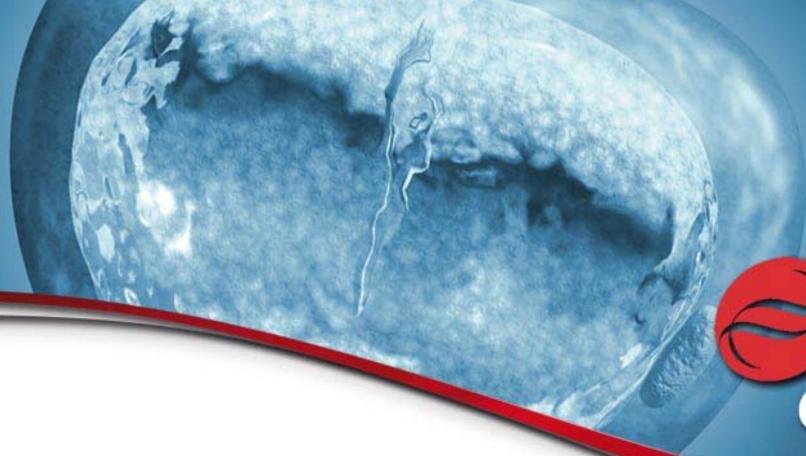
GnRH – Gonadotropin releasing hormone
ACT RII – Activin type II receptor

LH – Luteinizing hormone
FSH – Follicle stimulating hormone

Inhibin B controls FSH secretion via a negative feedback mechanism. This mechanism remains the subject of research².

Inhibin B binds to activin type II receptors (ACT RII) and thereby inhibits activin action. However, inhibin does not antagonise activin action in all target tissues. There is likely a specific binding factor for inhibin action. It has been shown that inhibin has specific binding sites in tissues where it acts, such as the pituitary gland³.

The primary role of inhibin B is the regulation of gametogenesis in both males and females. However, the mechanism of its function differs by sex.



Males^{2,4}

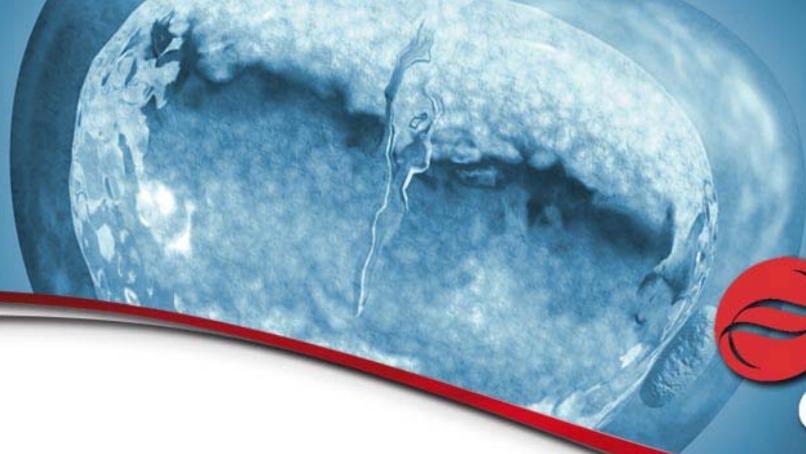
Inhibin B is the only inhibin form present in male circulation. The relationship between FSH and inhibin B varies throughout life, with a major switch in inhibin regulation around puberty. Inhibin B activity in children is governed by Sertoli cell proliferation and FSH. In adults, germ cells are the major determinant of inhibin B production.

Inhibin B levels are low but detectable in cord blood (see Fig.5 and 6, paragraph „Levels“). In the first week after birth, they increase to adult levels, then continue to rise to even higher levels around months 3-6. This early postnatal increase is presumably due to the activation of the hypothalamic – pituitary – testicular axis and indicates proliferation of Sertoli cells.

After the initial postnatal increase, inhibin B levels decline progressively to reach their nadir during years 3-6. Prior to puberty, inhibin B levels are independent on the presence of actively proliferating germ cells.

During puberty, the main controlling mechanism of inhibin B secretion switches from FSH to spermatogenesis. Basal inhibin B levels increase under FSH stimulation in the first pubertal stages, when the last wave of Sertoli cell proliferation occurs. Positive correlation between FSH and inhibin B levels is observed. However, when the negative feedback regulation loop is fully established (at Tanner stages III and IV of puberty), inhibin B and FSH levels correlate negatively.

In adults, FSH stimulates the production of inhibin B in the testis and inhibin B inhibits the secretion of FSH. In the presence of FSH, the prime regulator of inhibin B levels is spermatogenic status. When spermatogenesis is interrupted, inhibin B levels fall and FSH levels increase.



Females^{5,6}

In female circulation, both inhibin A and inhibin B play an important role in endocrine actions relating to the maturation of the hypothalamic-pituitary-gonadal axis, as well as in the growth and maturation of the ovaries.

Inhibin B levels are measurable in girls from the moment of birth, as in boys. However, they are generally lower in females than in males.

Inhibin B levels in newborn girls rise to (female) pubertal levels (see Fig.5 and 6, paragraph „Levels“). This early postnatal increase of inhibin B confirms its biological role (in cooperation with gonadotropins) in the activation of the hypothalamic-pituitary-gonadal axis, leading to growth and development of follicles during the neonatal period. High gonadal endocrine activity during the first months after birth is important for folliculogenesis.

After this initial postnatal increase, inhibin B levels decline progressively to reach their nadir during years 0.5-6. At the onset of puberty, the hypothalamic-pituitary-gonadal hormone axis is activated. Serum inhibin B levels increase markedly with pubertal development as a consequence of higher follicular development activity, which is induced by an increase in FSH in early puberty. In early puberty, the reproductive hormones (LH, FSH, estradiol, inhibin A, inhibin B) are all positively correlated to one another, reflecting the fact that levels of all these hormones increase as puberty progresses. With respect to inhibin B, the positive gonadotropin correlations of early puberty disappear in stage III. Stage III represents a period of consistently high ovarian follicular activity before the development of the adult menstrual cycle with ovulation and luteal phase.

The strong positive correlation between FSH and inhibin B levels reappears in stage IV, in conformity with FSH and inhibin B secretion in the follicular phase of the menstrual cycle (see Fig.8, paragraph „Levels“).

Inhibin B is essential to the menstrual cycle – together with other hormones (FSH, LH, AMH, estradiol, progesterone) it allows the regular and controlled cyclic maturation of follicles throughout a very important period of a woman's life – her childbearing age.

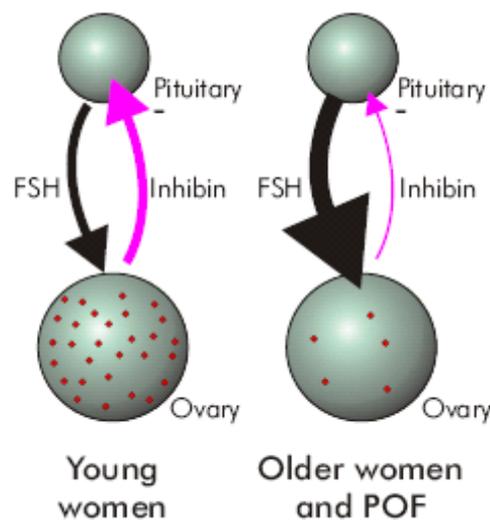
Inhibin B is produced by granulosa cells of small antral follicles in response to gonadotropin stimulation. The increased level of FSH results in the recruitment of a cohort of antral follicles from which the so-called „dominant“ follicle is selected. The granulosa cells of this „dominant“ follicle produce inhibin B, which suppresses FSH production by the pituitary gland; and estradiol, which suppresses

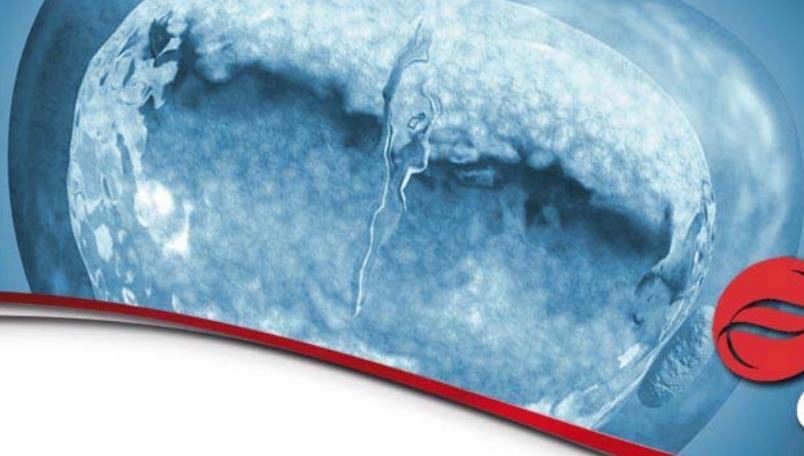


FSH production as well. Both inhibin B and estradiol have a positive feedback effect on LH, which allows the follicle to release an egg.

On the onset of menopause an initial decline in inhibin levels occurs, leading to an increase in FSH secretion. Increased FSH secretion causes increased follicular recruitment and leads to increased follicle depletion (see Fig.4). The Inhibin B level gradually decreases to very low levels after menopause, when the ovarian reserve is depleted.

Fig.4: Endocrine regulation of FSH and Inhibin B in younger and older women and in patients with premature ovarian failure (POF)





Levels

Physiological variation in Inhibin B levels is a function of both sex and age (see Fig.5 and Fig.6).

Fig.5: Inhibin B levels throughout the course of life

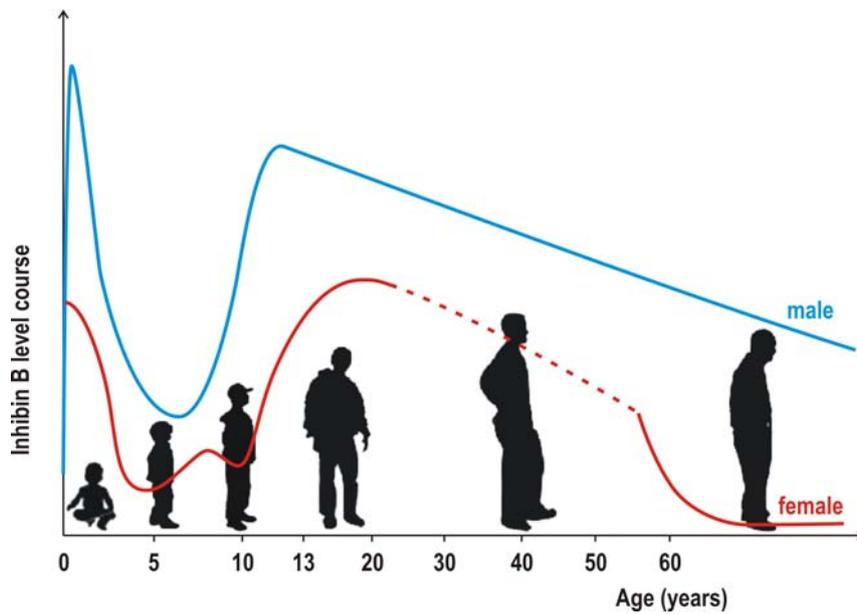
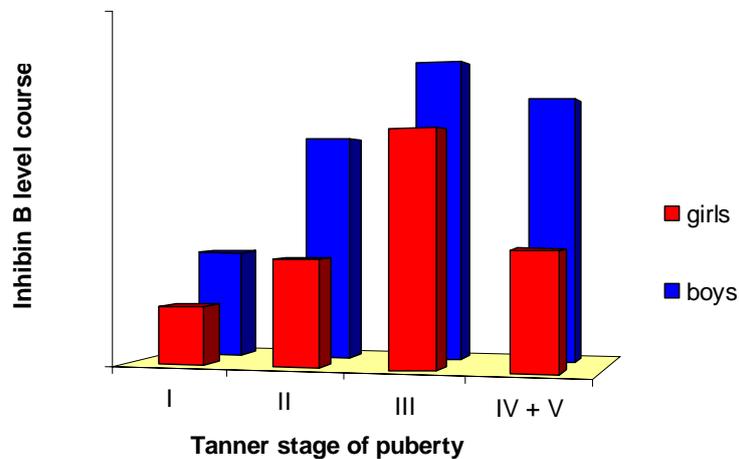
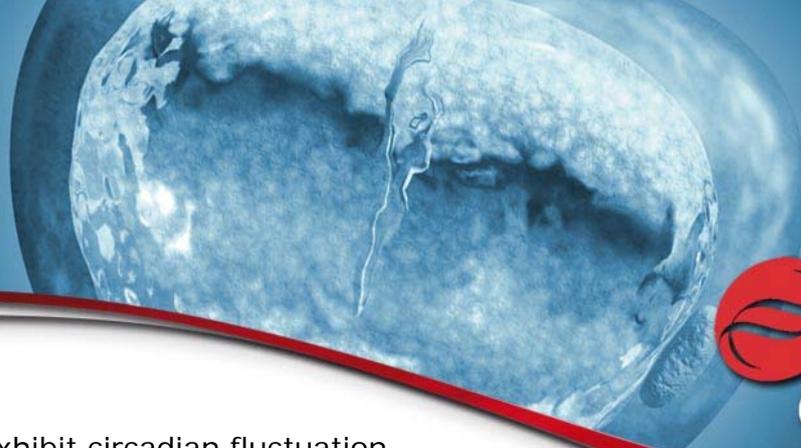


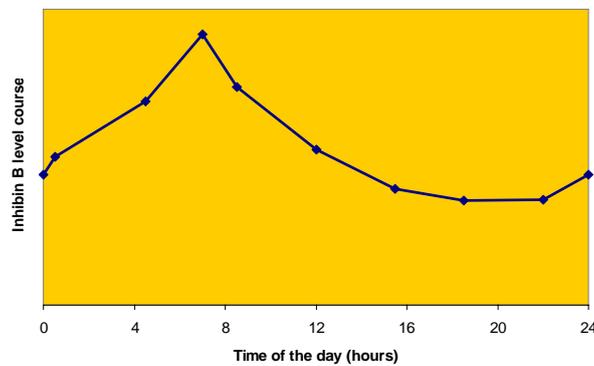
Fig.6: Inhibin B levels in different stages of puberty^{4,5}





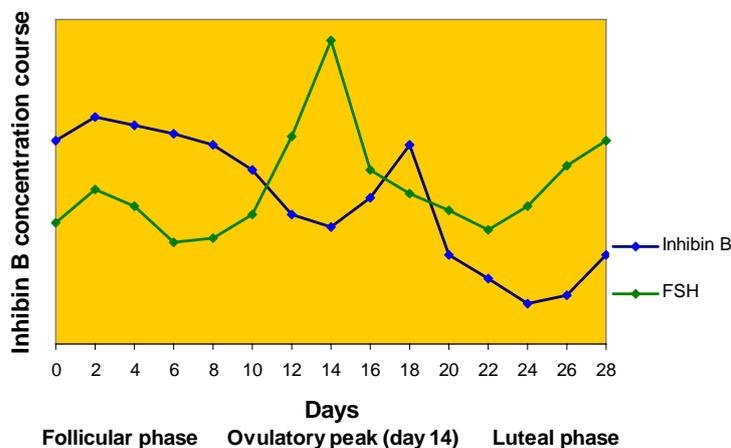
Inhibin B levels exhibit circadian fluctuation in healthy men, probably due to covariation with testosterone and estradiol levels. The general pattern shows higher values in the early morning and lower values in the late afternoon and the evening (see Fig.7). No evidence for circadian variation in women is available.

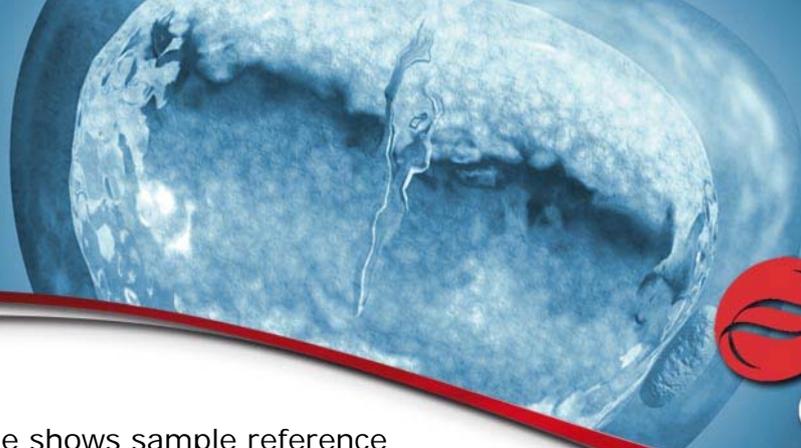
Fig.7: Inhibin B circadian variation in men⁷



On the other hand, variation in inhibin B levels during the menstrual cycle is very well documented. Serum inhibin B levels are highest at the follicular phase, fall in the periovulatory phase with a peak following FSH increase at ovulation, and are lowest in the mid- and end-luteal phase^{6,8}.

Fig.8: Inhibin B and FSH levels throughout the menstrual cycle⁸





The following table shows sample reference intervals of inhibin B levels taken from the Instructions for Use (IFU) of inhibin B Gen II ELISA (#A81303 Beckman Coulter). These are strictly for informational purposes, as appropriate reference levels vary according the assay used.

Specimen (serum)	Median Age	Reference interval (pg/mL)
Boys:	11	4 – 352
Girls:	11	ND – 83
Males:	35	25 – 325
Females:	30	ND – 341
Females 3rd day of cycle:	NA	ND – 273
Post-menopausal females:	74	ND – 4

ND – Non Detectable

NA – Not Applicable

Diagnostic utility – prospects and possibilities

Measurement of serum inhibin B provides a useful marker of reproduction status in both males and females. Abnormal inhibin B levels can be found throughout a broad spectrum of disorders, including:

Elevated inhibin B levels

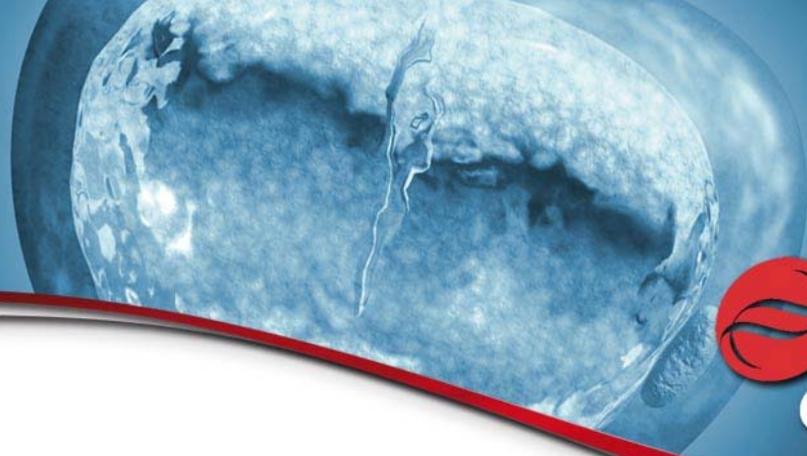


- some cases of precocious puberty
- granulosa cell tumors

Decreased inhibin B levels



- decreased Sertoli cell function
- decreased testicular volume
- inadequate sperm production
- cryptorchidism and ambiguous genitalia
- Kallmann ´s syndrome
- Klinefelter ´s syndrome
- bilateral orchidectomy
- polycystic ovary syndrome (PCOS)
- premature ovarian failure (POF)
- osteoporesis



Diagnostic utility – Practical applications

The hormone inhibin B is essential for correct spermatogenesis in males as well as for regulation of follicle maturation and menstrual cycle in females.

Determination of serum inhibin B levels is important in the evaluation of the gonad function and connected disorders.

In particular, Inhibin B determination is used in the following cases:

Evaluation of male fertility

Causes of male infertility can be divided into three major categories:

- failure, due to hormonal abnormalities, to produce an adequate number of sperm
- failure, due to testicular abnormalities, to produce an adequate number of normally functioning sperm
- inability to deposit sperm in the female genital tract due to ductal obstruction or abnormal sexual function.

Inhibin B is a direct marker of Sertoli cell function and spermatogenesis in adult males. Its level correlates with testicular volume and sperm density.

Very low levels of inhibin B indicate inadequate sperm production by the testis, which suggests e.g. a lower probability of success in assisted reproduction procedures such as TESE-ICSI (testicular sperm extraction – intracytoplasmic sperm injection).

Inhibin B serum levels are determined in conjunction with other hormones such as FSH, LH, testosterone and AMH.

Fig.9 shows inhibin B levels in healthy males and in males with various hypothalamic – pituitary – testicular axis disorders.

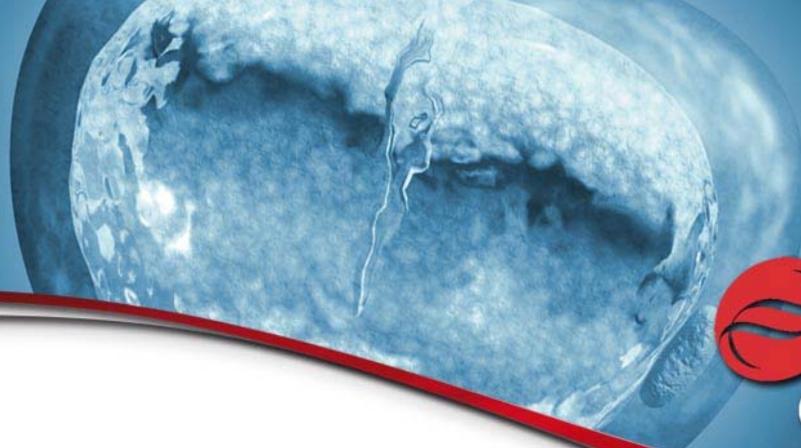
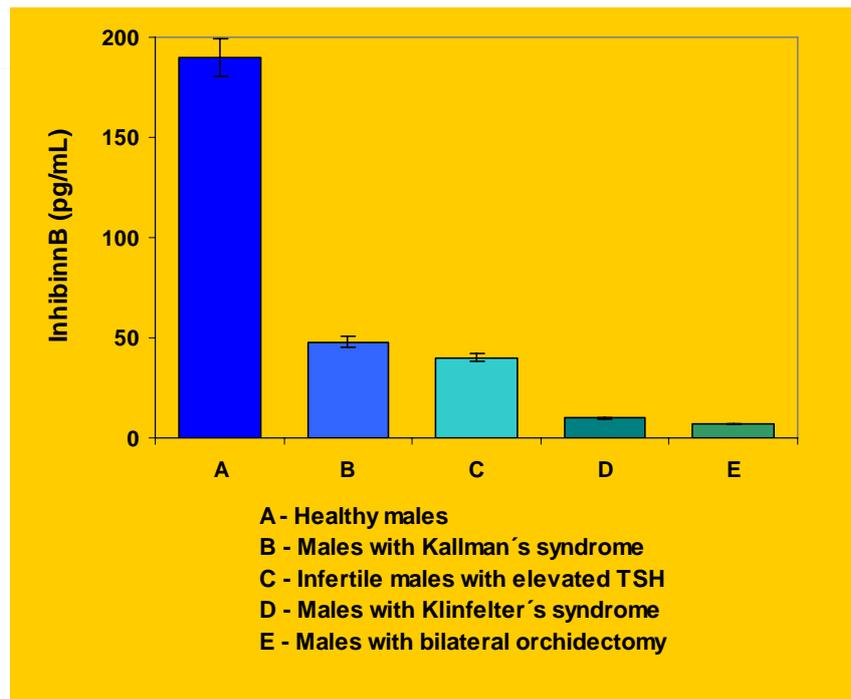


Fig.9: Inhibin B levels in healthy men and in men with various reproductive disorders⁹



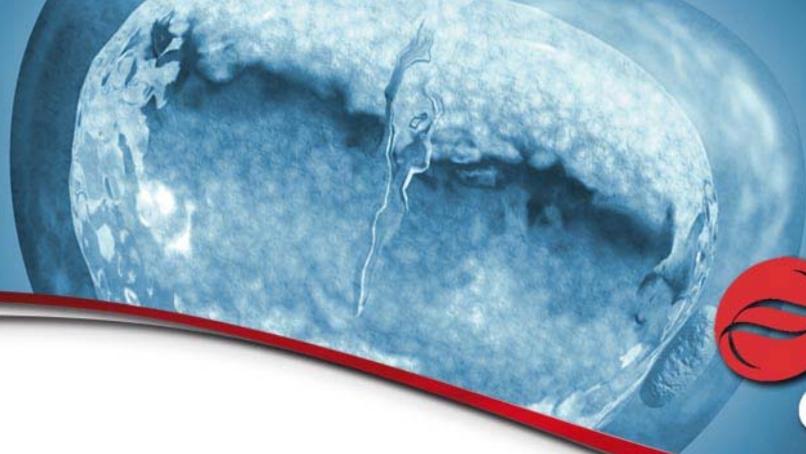
Determination of ovarian status in women

Inhibin B level reflects the continuous decline of the oocyte/follicle pool with age and thus ovarian ageing, premature ovarian failure (POF) and menopausal transition. It is used as a supplementary test in conjunction with FSH and AMH determination.

Inhibin B determination is also used (again with AMH and FSH) as a marker of ovarian responsiveness in patients undergoing assisted reproductive technology¹⁰.

Diagnosis and follow-up of polycystic ovary syndrome (PCOS)

The determination of serum inhibin B level is used in conjunction with AMH and FSH. Inhibin B levels are decreased in women with PCOS.



Diagnosis and management of granulosa cell tumors

Serum levels of inhibin B as well as inhibin A are increased in cases of granulosa cell tumors, thus they can help differentiate granulosa and mucinous cell tumors. They are measured in conjunction with CA-125¹¹.

Inhibin B and inhibin A levels are used also in post-operative follow-up of patients.

References

1. Welt C., Sidis Y, Keutmann H., Schneyer A.: Activins, inhibins, and follistatins: from endocrinology to signaling. A paradigm for the new millenium. *Exp. Biol. Med* 2002, 227(9), 724-752.
2. Meachem S.J., Nieschlag E., Simoni M.: Inhibin B in male reproduction: pathophysiology and clinical relevance. *Eur. J. Endocrinol.* 2001, 145, 561-571.
3. Robertson D.M., Hertan R., farnworth P.G.: Is the action of inhibin mediated via unique receptor? *Rev. Reproduct.* 2000, 5, 131-135.
4. Chada M., Prusa R., Bronsky J.,Kotaska K., Sidlova K., Pechova M., Lisa L.: Inhibin B, FSH, LH and Testosterone during childhood and puberty in males: changes in serum concentration in relation to age and stage of puberty. *Physiol. Res.* 2003, 52, 45-51.
5. Chada M., Prusa R., Bronsky J., Pechova M., Kotaska K., Lisa L.: Inhibin B, FSH, LH and Estradiol and their relationship to the regulation of follicle development in girls during childhood and puberty. *Physiol. Res.* 2003, 52, 341-346
6. Sehested A., Juul A., Holm Petersen J., Kold Jensen T., Muller J., Skakkeback N.E.: Serum Inhibin A and Inhibin B in healthy prepubertal, pubertal, and adolescent girls and adult women: relation to age, stage of puberty, menstrual cycle, FSH, LH and estradiol levels. *J. Clin. Endocrinol. Metab.* 2000, 85(4), 1634-1640.
7. Carlsen E., Olsson C., Holm Petersen J., Andersson A.-M., Skakkebaeck N.E.: Diurnal rhythm in serum levels of inhibin B in normal men: relation to testicular steroids and gonadotropins. *J. Clin. Endocrinol. Metab.* 1999, 84(5), 1664-1669.
8. La Marca A., Stabile G., Carducci Arsenio A., Volpe A.: Serum AMH throughout the human menstrual cycle. *Hum. Reprod.* 2006, 21(12), 3103-3107
9. Anwalt B.D., Bebb R.A., Matsumoto A.M., Groome N.P., Illingworth P.J., McNeilley A.S., Bremmer W.J.; Serum Inhibin B Levels Reflect Steroli Cell Function in Normal Men and Men with testicular dysfunction; *J. Clin. Endocrinol. Metab.* 1996, 81 (9),3341-3345
10. Byung Chul Jee, Seung Yup Ku, Chang Suk Suh, Ki Chul Kim, Won Don Lee, Seok Hyun Kim. Serum AMH and Inhibin B levels at ovulation triggering day can predict the number of Immature oocytes retrieved in IVF. *J. Korean. Med. Sci.* 2008, 23, 657-661.
11. Robertson D.M., Cahir N., Burger H.G., Mamers P., McCloud P.I., Pettersson K., McGuckin M.: Combined inhibin and CA125 assays in the detection of ovarian cancer. *Clin. Chem.* 1999, 45, 651-658.